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Proposed New USP General Chapter: The Analytical Procedure Lifecycle ⟨1220⟩

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ABSTRACT

An analytical procedure must be demonstrated to be fit for its intended purpose. It is useful to consider the entire lifecycle of an analytical procedure, i.e., its design and development, qualification, and continued verification. The current concepts of validation, verification, and transfer of procedures address portions of the lifecycle but do not consider it holistically. The purpose of this proposed new chapter is to more fully address the entire procedure lifecycle and define concepts that may be useful. This approach is consistent with the concept of quality by design (QbD) as described in International Council for Harmonisation (ICH) Q8-R2, Q9, Q10, and Q11. The lifecycle approach can potentially be applied to all procedures, although the level of effort should be consistent with the complexity and criticality of the procedure.

INTRODUCTION

This *Stimuli* article provides the framework for *The Analytical Procedure Lifecycle* ⟨1220⟩. This article describes the current thinking of the USP *Validation and Verification Expert Panel* which advises the *General Chapters—Chemical Analysis Expert Committee* with regard to future trends in analytical procedures development, qualification, and continued monitoring. These concepts are described here for the purpose of offering an alternative approach to the classical analytical validation and subsequent verification and transfer, viewing these activities as a continuum and closely interrelated rather than as discrete actions. This enhanced approach potentially offers several advantages, including:

- Improved understanding of the procedure and control of sources of variability, which are linked to the intended use of the procedure as described in the analytical target profile (ATP)
- Procedures that are more robust, resulting in fewer failures during use and during qualification in a new laboratory
- Reduction of overall resources required for a new or revised procedure. The levels of effort, formality, and documentation should be commensurate with the level of risk
- Identification of adverse trends, allowing proactive measures and facilitation of continued improvements and change control through continued monitoring

The *Validation and Verification Expert Panel* considers this lifecycle approach to still be evolving, as International Council for Harmonisation (ICH) Q8, Q9, and Q10 concepts are being adopted by the analytical community. Therefore, it is advisable to provide guidance on how to incorporate lifecycle management strategies into analytical procedures, which will increase flexibility in demonstrating the fitness of analytical procedures while leaving the option open to use the classical approach described in *Transfer of Analytical Procedures* ⟨1224⟩, *Validation of Compendial Procedures* ⟨1225⟩, and *Verification of Compendial Procedures* ⟨1226⟩. In addition to offering a preview of the proposed general chapter, the General Chapters—Chemical Analysis Expert Committee and the Validation and Verification Expert Panel are seeking specific input from users in the pharmaceutical industry regarding the following questions:

1. Would a general chapter on the lifecycle approach be valuable?
2. Is the information presented herein sufficient for implementation of an analytical procedure under the quality by design (QbD) approach?
3. Would incorporation of references to statistical tools, either in this chapter or in another chapter, be valuable?
4. Can you provide input or approaches that would improve this proposed general chapter?

The content and scope of the proposed general chapter will be refined on the basis of responses to this *Stimuli* article. Because stakeholders may have differing views, the objective of this *Stimuli* article is to identify and build areas of consensus that may be included in ⟨1220⟩.

THE LIFECYCLE APPROACH

Reportable values generated using qualified analytical procedures provide the basis for key decisions regarding compliance of a test article with regulatory, compendial, and manufacturing limits. These values may be applied against decision rules that provide a prescription for the acceptance or rejection of a drug product or drug substance. This is based on the analytical measurement, the uncertainty of the measurement, and the acceptance criteria, taking into account the acceptable level of risk of making a wrong decision.

Application of lifecycle management concepts to analytical procedures is based on QbD and provides an opportunity to use the knowledge gained from the application of scientific approaches and apply that knowledge to reportable values generated when using the analytical procedure. The concept of QbD is understood as a systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8). The quality risk management (QRM) for an analytical procedure is a systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the analytical procedure lifecycle. It is important to understand and control sources of variability to ensure that measurement uncertainty is aligned with the decisions that will be made using results generated by an analytical procedure.

Lifecycle Stages

In order to provide a holistic approach to controlling an analytical procedure throughout its lifecycle, one can use a three-stage concept (see *Figure 1*) that is aligned with current process validation terminology:

Stage 1: Procedure Design and Development

Stage 2: Procedure Performance Qualification

Stage 3: Continued Procedure Performance Verification

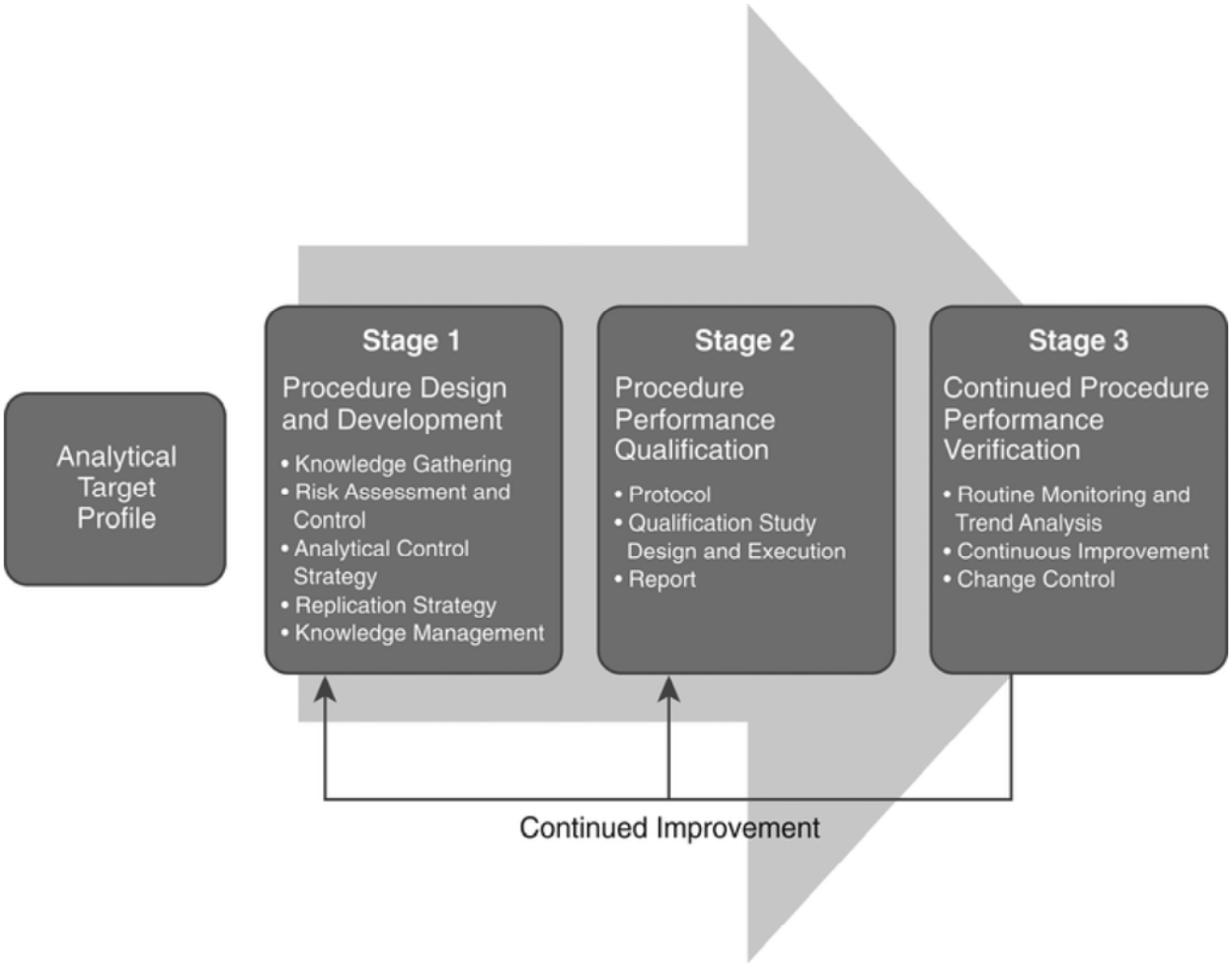

Figure 1. The analytical procedure lifecycle.

Analytical Target Profile

A fundamental component of the lifecycle approach to analytical procedures is having a predefined objective that stipulates the performance requirements for the analytical procedure. These requirements are described in the ATP. The ATP states the required quality of the reportable value produced by an analytical procedure in terms of the target measurement uncertainty (TMU). ATP criteria are derived from external requirements and not only from the performance of the analytical procedure. The acceptable level of risk of making an incorrect decision is considered when establishing an ATP. The reportable value may be the mean of multiple analytical results, if there is a defined replication strategy that is documented in the procedure. TMU is the maximum uncertainty that can be associated with a reportable result while still remaining fit for its intended purpose. TMU is a consolidation of the uncertainty from all sources, as illustrated in *Figure 2*.

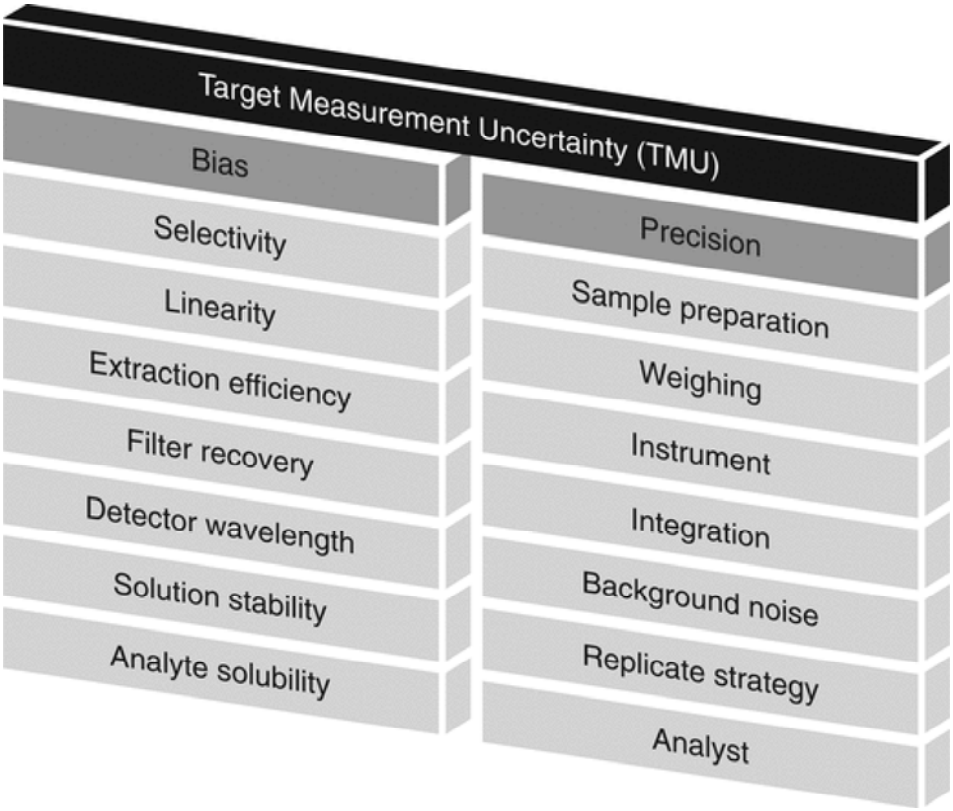

Figure 2. Consolidation of attributes contributing to TMU through accuracy (bias) and precision.

When establishing an ATP, the following should be considered, where relevant:

- Sample to be tested
- Matrix in which the analyte will be present
- Allowable error for the measurement as assessed through accuracy (bias) and precision, both of which make up the TMU
- Allowable risk of the criteria not being met (proportion of results that are expected to be within the acceptance criteria)
- Assurance that the measurement uncertainty and risk criteria are met

The current ICH and USP validation guidance can be incorporated into an ATP, with emphasis on the quality of the reportable value as shown for a drug product assay (*Example 1*).

EXAMPLE 1: ATP #1

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] with the following requirements for the reportable values: Accuracy = 100% ± D% and Precision ≤ E%.

The ATP inputs for [analyte], [description of test article] and [*x, y, z*] (which may be impurities or excipients) can be specified. Values for *D* and *E* should be specified. For example, *D* may be expressed as a percentage of label claim and *E* may be expressed as a percentage of relative standard deviation (%RSD). Alternative units are acceptable as long as they are unambiguous.

Advantages of this approach to an ATP are:

- The ATP is easy to understand, calculations are relatively straightforward, and data are easy to assess for ATP conformance by non-statisticians.
- The ATP includes criteria for accuracy (bias) and precision of the reportable value and is therefore linked to the quality of the reportable values.
- This approach encourages understanding and control of sources of variability (defined control strategy).

Limitations of this approach include:

- Accuracy (bias) and precision are assessed separately so that the TMU of the results is not explicitly defined.
- This approach does not quantify the risk of making a wrong decision by including probability and confidence criteria. However, while the level of risk is not transparent, risk can be controlled through the alignment of specifications and accuracy (bias)/precision criteria such that reportable values that are within specification have a low probability of being on an edge of failure with respect to clinical relevance.

In current approaches, criteria for accuracy (bias) and precision are often established based on generally accepted industry practices using default criteria. However, in a QbD approach, these criteria are aligned with the specification and product and process needs, and the criteria focus on the reportable value.

EXAMPLE 2: ATP #2

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] so that the reportable values fall within a TMU of ±C%.

The ATP inputs for [analyte], [description of test article] and [*x, y, z*] (which may be impurities or excipients) can be specified.

This example contains criteria for the TMU, (±*C*%), which is directly linked to the results generated by the procedure. The TMU considers the acceptable difference between the measured reportable value and the target value and can be established based on a fraction of the specification range.

The ATP serves as a reference point for assessing the fitness of an analytical procedure, not only in the development phase but also during all changes within the analytical lifecycle. Note that the ATP is not linked to a specific analytical procedure. Thus, it is conceivable that more than one analytical procedure could meet the requirement of an ATP, and that an alternate procedure that meets the requirement stated in the ATP would be acceptable.

For procedures that do not already have an ATP, including existing procedures in compendial monographs, one can be constructed. For instance, the ATP may be based on product acceptance criteria and any existing requirements for the analytical procedure as stated in the monograph.

In assessing new or existing procedures for their ability to meet an ATP, analysts may use statistical methods for analyzing prospectively designed studies. In the case of existing procedures for which significant data are available, statistical procedures for retrospective evaluation of historical data, such as stability data, laboratory investigations, check samples/controls, release data, and others may be used. The level of variability present in the historical data may trigger additional studies that aim to understand and reduce or eliminate sources of variability and also improve the data quality by means of an optimized control strategy to meet the ATP.

STAGE 1: PROCEDURE DESIGN AND DEVELOPMENT

Knowledge Gathering

When the need for a procedure is identified, relevant information should be gathered prior to conducting laboratory studies. Such information may include known chemical structures, solubility, reactivity, and stability of the molecules of interest. A literature search may also be useful to understand how the procedure has been applied or modified by others. The intended purpose and fitness for routine use must always be considered. Any relevant information identified during the knowledge-gathering stage—such as the range over which the procedure will be used, criteria for run time, equipment type, and other information—is also considered during the design and development stage. However, this information is not captured in the ATP.

Once the knowledge-gathering phase is complete, the information is used to select an appropriate technology and procedure likely to meet the requirements defined in the ATP.

Risk Assessment Evaluation and Control

The objective of a risk assessment is to develop understanding of procedure variables and their impact on the reportable value, which will assist in the development of a control strategy.

For example, tools such as process maps and Ishikawa diagrams (fishbone diagrams) may be used, in addition to prior knowledge, to provide structure to a brainstorming and information-gathering exercise to identify variables. The attributes shown in *Figure 2* may serve as a useful starting point. It is important to consider all steps in the analytical procedure, including development of standard and test sample preparation. It is important to ensure that the sample preparation step does not cause the analyte to undergo any significant (uncontrolled or unintended) changes in its relevant properties from the moment of sampling to the time when the actual analysis is carried out. Sample preparation conditions are frequently a source of procedure variability and/or bias and its influence in the performance of the procedure should be investigated. In the case of sample preparation that involves dissolving a sample prior to analysis, systematic extraction studies should be performed to ensure robust, rugged, and complete extraction/dissolution. It is also important to investigate sources of variability and systematic bias during Stage 1 so that they may be eliminated or controlled during routine use of the procedure.

Besides accuracy (bias) and precision, which are defined in the ATP, experiments may include other method-specific performance attributes known as traditional validation characteristics (see *Figure 2*). However, these characteristics are eventually consolidated into the ATP attributes.

Risk-assessment tools may be used to prioritize which variables should be studied to evaluate their impact on the reportable results. Results from experiments investigating variables can be used to develop and justify the control strategy.

Design of experiments (DOE) is a fundamental methodology for the QRM process. It is a systematic method to determine the relationships between variables affecting a process, and it is used to find cause-and-effect relationships. This information is needed to manage process inputs in order to optimize the output of the procedure. Multi-factor studies are a powerful way to develop understanding, although single-factor studies are also appropriate in some cases. DOE also utilizes statistical data treatment, which allows clear determinations regarding the significance of a variable and/or its interactions towards the output.

Analytical Control Strategy

The analytical control strategy is a planned set of controls, which is the output of the QRM process. It is derived from an understanding of both the requirements for the reportable value established in the ATP and the understanding of the analytical procedure as a process.

The variables that need to be controlled and their acceptable ranges (from the risk assessment and subsequent experiments) should be explicitly specified in the procedure. Typical controls may include limits for variability of calibration and between replicates; instructions for environmental controls (light, temperature, and humidity); sample solution stability; and, for chromatographic methods, system suitability requirements such as sensitivity, resolution, etc. In addition, the controls may include variables and aspects related to the sample, sample preparation, standards, reagents, the facility, equipment operating conditions, the format of the reportable value (i.e., number of replicates), and the frequency of monitoring and control.

A replication strategy may be applied to reduce the random variability of the mean (reportable value). It should be noted that increasing the number of replicates will only reduce the random variability corresponding to the step that is replicated. For example, increasing the number of injections will reduce the injection variance, whereas increasing the number of sample preparations will reduce the variance associated with sample preparation.

The analytical control strategy plays a key role in ensuring that the ATP is realized throughout the lifecycle. Different control strategies may be required in different labs or when using different equipment.

Knowledge Management

Knowledge management for analytical procedures is a systematic approach to acquiring, analyzing, storing, and disseminating information, and is an important factor in ensuring the ongoing effectiveness of the control strategy. Knowledge management should include, but should not be limited to, development activities, technology transfer activities to internal sites and contract laboratories, qualification and monitoring studies over the lifecycle of the analytical procedure, and change management activities. The knowledge gathered to develop the procedure understanding should be collected in a repository and shared as needed to support implementation of the control strategy across sites that use the analytical procedure. Changes and improvements to a qualified analytical procedure should be made through the change control system.

Preparing for Qualification

Before beginning a qualification study, data collected during Stage 1 can be assessed to provide supporting evidence for the absence of significant bias and a confirmation that the precision is at an appropriate level, as well as other pertinent analytical characteristics. Although bias and precision estimates at this stage do not guarantee that a qualification study will be successful, they can flag a potentially problematic procedure.

As an integral part of preparation for laboratory qualification to execute a compendial procedure or a procedure from another site, the process of QRM should be carried out, and the control strategy of the procedure should be verified or expanded to ensure that the requirements of the ATP are met.

STAGE 2: PROCEDURE PERFORMANCE QUALIFICATION

Once an ATP has been established and design activities are completed with appropriate minimization of bias and uncertainty, knowledge is compiled and documented. A procedure control strategy is proposed and the performance of the procedure is ready to be qualified. The purpose of qualification is to confirm that the procedure generates reportable values that meet the ATP criteria and remain appropriate for the testing of the

product in the environment where it will be used. The laboratory that will be using the procedure to generate results should perform the qualification study.

The protocol for the qualification study should be documented and should include (but is not limited to) the ATP; method-specific performance attributes and acceptance criteria; a description of or reference to the procedure including its control strategy; a description of the experiments including the number of standards, test sample, and series analysis that will be performed; and the statistical approach to be used to analyze the data.

The analytical control strategy may be refined and updated as a consequence of any learning from the qualification study. For example, further controls may be added to reduce sources of variability that are identified in the routine operating environment in an analytical laboratory, or replication levels (multiple preparations, multiple injections, etc.) may be modified based on the uncertainty in the reportable value.

Qualification strategies will depend on the criteria described in the ATP and on the intended use of the procedure.

STAGE 3: CONTINUED PROCEDURE PERFORMANCE VERIFICATION

Stage 3 of the procedure lifecycle ensures that the analytical procedure remains in control, i.e., this stage maintains the established performance level and thus continues to meet ATP criteria. Therefore, the ATP is used as a reference point for the performance of the procedure during Stage 3 of the lifecycle of the analytical procedure.

This stage includes both routine monitoring and evaluation of the analytical procedure's performance after changes to determine if the analytical procedure continues to be fit for purpose.

Routine Monitoring

Effective monitoring of an analytical procedure provides confidence that the reportable value generated is fit for purpose.

This stage should include an ongoing program to collect and analyze data that relate to analytical procedure performance. Monitoring may include tracking analytical results, system suitability failures, out-of-specification or out-of-trend investigations, stability trends, or other parameters as appropriate. If the monitoring data indicate that the procedure is not in control, an investigation should be performed with a goal of identifying the root cause. Corrective and preventive action should be taken to ensure that the analytical control strategy is updated in the analytical procedure.

A routine monitoring program therefore needs to be designed to:

- Ensure that the performance of the procedure or of appropriate steps (for example, injection and sample preparation variability) maintains an acceptable level over the procedure lifetime. (This is done to conclude that the reportable values produced by the procedure continue to meet the ATP requirement.)
- Provide an early indication of potential procedure performance issues or adverse trends.
- Identify any changes required to the analytical procedure.

Changes to an Analytical Procedure

During the lifecycle of a pharmaceutical product, both the manufacturing process and the analytical procedure are likely to experience a number of changes because of continued improvement activities or the need to operate the method and/or process in a different environment (method transfer).

Depending on the degree of change, the actions required to qualify the change will be different. Some examples are given below:

- A change to a procedure variable to a value within the range that was previously qualified would not require additional experimentation to qualify the change.
- A change to a procedure variable to a value outside the range that was previously qualified to produce fit-for-purpose data would require performance of a risk assessment. The risk assessment should consider which procedure performance characteristics may be impacted by the change and should then perform an appropriate procedure performance qualification study to confirm that the change does not impact the method's ability to meet the ATP.
- A change to a new laboratory would require review of the risk assessment and an appropriate qualification study (which might include comparability testing or a reduced or full requalification).
- A change to a new procedure/technique would require performance of appropriate development and qualification activities (Stages 1 and 2) to demonstrate conformance of the new procedure to the ATP.
- A change impacting the ATP, e.g., a specification limit change or a need to apply the procedure to measure levels of analytes not considered in the original ATP, would require an update to the ATP and a review of the existing procedure design and qualification data (Stages 1 and 2) to determine whether the procedure will still meet the requirements of the new ATP.

The level of activities required to confirm that a changed analytical procedure is producing fit-for-purpose data will depend on an assessment of 1) the risk associated with the change, 2) the knowledge available about the procedure, and 3) the effectiveness of the control strategy. It is recommended that for all changes, a risk assessment should be carried out to determine the appropriate level of activities required. The aim of the exercise is to provide confidence that the modified method will produce results that meet the criteria defined in the ATP. This may be assessed by considering the risk that the change in the method will have on the accuracy (bias) and precision of the reportable value. Risk assessment tools can be used to provide guidance on what actions are appropriate to verify that the method is performing as required.

Applying a lifecycle approach to analytical procedures should ensure that quality objectives for the reportable values are met on a consistent basis.

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